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Anatomical Detectable Tuberculosis in Victims of Unnatural Death in Kyoto and Mathematical Considerations of the Frequency of Tuberculous Primary Infection and Exogenous Reinfection.

By

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(I) Introduction.

It has been believed from the beginning of the 20th century that the populations of large cities in North america and Europe were widely infected with tuberculosis in the adult age group. With the pathological-anatomical in vestigation, tuberculosis was detected at a very highrate by several pathologists, for instance, anatomical tuberculosis was pruved in 97% in Zürich by Nägeli (1900), 100% St. Louis by Opie (1917) and in 91-92% in Dresden by Schüramann (1926).

But the studies of Straub (1937) showed that anatomical tuberculosis among Chinese and Javanese on the east coast of Sumatra was less frequent than among Europeans in Prague and Amsterdam. The clinical research of Malmros and Hedvall (1938) in south Sweden and that of Kumagai (1938) at Sendai city in north-east Japan also showed that tuberculous primary infection occurred very often among the populations even in the adult age group, and these investigators insisted on the importance of primary infection for the development of pulmonary tuberculosis in the adult.

We can also note that anatomical tuberculosis in adults was detected rather seldom (55%) in a semi-rural district, Hagerstown in Maryland U.S.A. by Lande and Wolff (1938–1944), while in large cities in U.S.A. it is fairly widespread: for instance, 91% in Baltimore (1938-1940, by Carnes) and 65% in Buffalo (1932-1950, by Terplan).

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Table 1. Anatomical tuberculosis in the adult.

Date of publication or Research	Investigator	Locality investigated. (Population in 1921)	Age	Positive rate of detected anatomical tuberculosis.
1900	Nägeli	Zürich, Switzerland. (200,000)	Adults	97%
1917	Opie	St. Louis, U.S.A. (757,000)	0-18 18-	24% 100%
1926	Schürmann	Dresden, Germany. (548.000)	0-18 19-30 31-50	58% 91% 92%
1937	Straub	Prague, Czecho-Slovakia. (541,000)	19-	93%
		Amsterdam, Holland. (617,000)	19-	89%
		East Coast, Sumatra. Chinese	19-	70%
		East Coast, Sumatra. Javanese	19-	47%
1938-1940	Carnes	Baltimore, U.S.A. (558,000)	0-19 20-	16% 91%
1938-1944	Lande & Wolff	Hagerstown, Maryland, U.S.A. (16,000)	0-19 20-	8% 55%
1949-1951	Yamori, Mori, Deme & Uno	Kyoto, Japan. (540.000)	0-14 15-19% 20-	38% 63% 82%
1932-1935 1936-1941 1942-1945 1946-1950	Terplan	Buffalo, U.S.A. (424,000)	19-90% 19-90% 19-90% 19-90%	85% 85% 83% 65%

So we can suppose that a high or low incident of anatomical tuberculosis in any one locality would depend mostly upon the density of the populalion, that is, a high frequency of anatomical tuberculosis may be due to the prevalent infection with tuberculosis and consequently the frequency of exogenous reinfection in a locality may also be due to the prevalence of tuberculous infection in the population.

Accordingly, in regard to the rate of tuberculous infection among different populations we wish to make some mathematical treatments on the total sum of the primary infection and exogenous reintection varying with the advance in age. And by pathological-anatomical examinations of victims of sudden death we also want to know the epidemiology of tuberculous infection in Kyoto city.

(II) Research on anatomical tuberculosis and Mantoux-tuberculin testing in Kyoto city.

The materials we used were obtained at autopsy from 342 victims of sudden death in Kyoto city from May 1949 to May 1952. We considered caseous and calcified foci and lesions with epithelioid and Langhans's giant cells as tuberculous lesions. Cicatrized foci without caseation, calcification or specific cells were not regarded assumptively as tuberculous lesions for reason that they occur frequently from non-tuberculous inflammations. We sliced maticulously lungs, lymph nodes, liver, spleen, kidneys, mesentery intestine, neck organs and uro-genital organs into very thinsections and searched for tuberculous lesions.

Of 264 autopsies, there were 271 individuals who had anatomically detectable tuberculous lesions, usually in minimal extent. The age distribution of anatomical tuberculosis we represent in Table 2.

Table 2.
The age distribution of anatomical tuberculosis found at autopsy in victims of unnatural death in Kyoto. (1949-1952).

Age	0 – 14	15 – 19	20 – 24	25 – 29	30 – 34	35 – 39	40 – 44	45 – 49	50 – 54	55 – 59	60 –
Number of cases examinated	8	26	83	59	27	21	25	18	13	22	40
Number with anatomical tuberculosis	3	15	61	47	24	19	20	18	13	17	34
Rate of anatomical tuberculosis	37.5%	57.7%	73.5%	79.7%	88.9%	90.5%	80.0%	100%	100%	77.3%	85%

Next we examined the pathological properties of the primary complex of every case of anatomical tuberculosis in order to know the elapsed time from occurrence of primary infection to death. We classified them into following 4 groups: caseation, chalky change (cretification), pebble development in the calcified focus and complete calcification (stony hard). The results of our examinations are represented in 3 age-groups in Table 3.

Teble 3.
Property of primary complex of anatomical tuberculosis in Kyoto.

Age	case number	caseation	chalky change (cretification)	pebble development in calcified focus	complete calcification (stony hard)
0 – 19	18	5 (28%)	0 (0%)	1 (6%)	12 (67%)
20 – 39	151	39 (26%)	11 (7%)	13 (9%)	88 (58%)
40 –	102	21 (21%)	6 (6%)	7 (7%)	68 (67%)

A state of caseation in the primary complex may be deduced to show a rather short duration between the occurrence of the primary infection and death, so we can suppose from Table 3 that the occurrence of primary infection in the adult and abvanced age is not rare in Kyoto city and is found usually at nearly the same, or even somewhat greater frequency as in the infant and adolescent.

In order to compare the results of anatomical tuberculosis discovered at autopsy with those of the tuberculin-Mantoux test, we could obtained statistical information on the tuberculin test on the general population in Kyoto city through the kindness of Dr. K. Naito (chief of the Prevention section, Sanitary Bureau of Kyoto city) and also on the population of a semi-rural

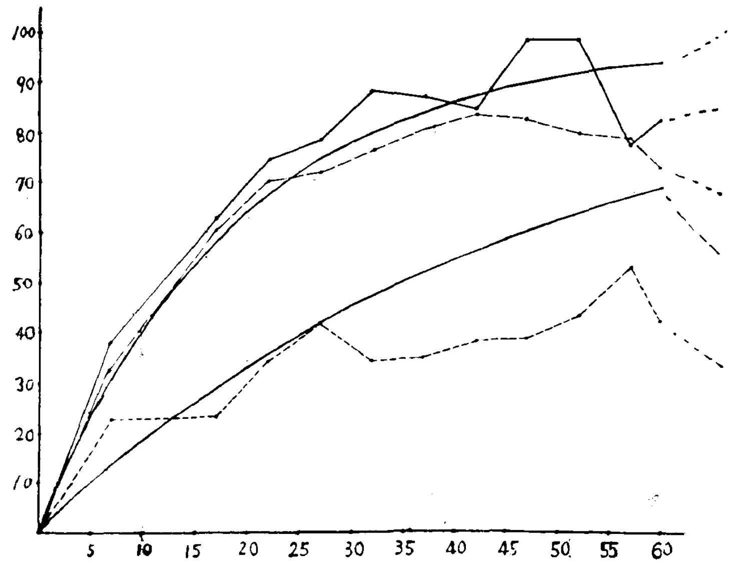
Table 4.

Results of tuberculin-Mantoux test on the general population in Kyoto city (1949-1950) and in semi-rural Oomi-Hachiman district (1950).

	Age	0 - 14	15 - 19	20 - 24	25 - 29	30 - 34	35 - 39	40 - 44	45 - 49	50 - 54	55 - 59	60 -
Tuberculin test in Kyoto city (27,585 individuals	Number of examinations	11832	3429	3789	2614	1551	1348	1074	805	562	305	276
	Number of positive reactors	3804	2071	2671	1888	1196	1100	907	674	456	245	204
	Rate of positive reactors	32.1%	60.4%	70.5%	72.2%	77.1%	81.6%	84.5%	83.7%	81.1%	80.3%	73.9%
Tuberculin test in Oomi-Hachiman (17,900 individuals	Number of examinations	920	4671	4093	3540	882	885	822	825	433	421	388
	Number of positive reactors	213	1090	1408	1493	309	314	321	324	192	227	146
	Rate of positive reactors	22.9%	23.3%	34.4%	42.2%	35.0%	35.5%	39.1%	39.3%	44.3%	53.9%	43.2%

district, Oomi-Hachiman (a town of about 15,000 population plus its rural surroundings) through the kindness of Dr. S. Takebe (chief of the Oomi-Hachiman Health-Center). Figures are shown in Table 4.

The relation of anatomical tuberculosis to the tuberculin test is represented in Figure 1.



$Pn\left(\frac{1}{20}\right)$. Standard curve under infection rate $\frac{1}{20}$.

Curve of positive anatomical tuberculosis in Kyoto city (1946-1952)

Curve of positive tuberculin test in Kyoto city (1949-1950)

$Pn\left(\frac{1}{50}\right)$. Standard curve under infection rate $\frac{1}{50}$.

Curve of tnberculin test in Oomi-Hachiman (1950)

$Pn\left(\frac{1}{20}\right)$ and $Pn\left(\frac{1}{50}\right)$:
It will be explained afterward.

We can easily see from this figure that the age distribution of the positive rate of anatomical tuberculosis is almost the same as that of positive tuberculin tests on the general population in Kyoto city. But strictly speaking, we can see that the fomer keeps a higher value than the latter. Now the adult anatomical tuberculosis (over 20 years old) in Kyoto city is positive in 82%, which can be considered approximately the same as the results of Terplan, Carnes, Schürmann and Straub when they examined large cities in U.S.A. and Europe, and to be far from that of Lande-Wolff and Straub when they examined semirural districts in U.S.A. or Sumatra. From our results also we may suppose that tuberculous infection is rather prevalent in large cities and is not so conspicuous in rural or semi-rural districts in Japan. So it may be better in considering tuberculous infection to make a distinction between the dense population of great cities and the sparse population of rural or semi-rural district.

(III) Mathematical treatment of the frequency of tuberculous primary infection and exogenous reinfection.

If the rate of tuberculous infection per year is designated as (a) and ages after birth as (n), the total of non-infected individuals will be reduced from 1 to (1-a) at the end of a year and similarly reduced to (1-a) (n) years after birth. And when the total of individuals at (n) years of age infected with tuberculosis more than once, under the definite infection rate per year (a), during (n) years from birth is designated as $P_n(a)$, it can be understood that following equation is correct.

$$P_n(a) \quad = \quad 1 \quad - \quad (1-a)^n \cdots\cdots\cdots\cdots\cdots\cdots (A)$$

total number of individuals at (n) years of age.

total number of individuals at (n) years of age who have not been infected with tuberculosis during (n) years after birth.

Now we can find that the positive rate of total individuals who primary infection is increased in every year under the value given by the formula (A). Then we can see that the yearly chenges of positive rate of anatomical tuberculosis in victims of sudden death and that of the tuberculin test of general population in Kyoto city are very close given by $P_n(a)$, when (a) is decided as $\left(\frac{1}{20}\right)$. (see figure 1) And we can also see that the yearly changes in the rate of positive tuberculin tests in the semi-rural Oomi-Hachiman district are somewhat higher in chidhood and lower in the adolescent and adult ages than the value as given by $P_n(a)$, when (a) is decided as $\left(\frac{1}{50}\right)$ (see figure 1)

Next, if the total of individuals at (n) years of age who has exogenous reinfection or superinfection more than twice, under the definite infections rate per year (a), during (n) years after birth is desfinated as $R_n(a)$, it can be understood that the following mathematical equations are correct.

$R_n(a)=R_{n-1}(a)$ ····················· number of individuals who have aleady infected exogenously more than twice until the end of (n-1) years of age after birth.

$+a[P_{n-1}(a)-R_{n-1}(a)]$······ number of individuals who have the second exogenous tuberculous infection during the course of a year from (n-1) to (n) years of age among people who already had the first tuberculous infection before the end of (n-1) years of age after birth.

$+a^2[-1P_{n-1}(a)]$ ··········· number of individuals who have the first and second exogenous tuberculous infection with in the course of a year from (n-1) to (n) years of age among people who have never been infected with tuberculosis until the end of (n-1) years of age after birth.

$$R_n(a)=R_{n-1}(a)+a[\{1-P_{n-1}(a)\}a+P_{n-1}(a)-R_{n-1}(a)]$$

hereupon $\{1-P_{n-1}(a)\}a+P_{n-1}(a)=P_n(a)$

$$R_n(a)=R_{n-1}(a)+a[P_n(a)-R_{n-1}(a)]$$

that is $R_n(a)=aP_n(a)+(1-a)R_{n-1}(a)$

$$=a[1-(1-a)^n]+(1-a)R_{n-1}(a)$$

hence $R_n(a)\quad -(1-a)R_{n-1}(a)=a\quad -a(1-a)^n \quad\cdots\cdots(1)$

likewise as above $(1-a)R_{n-1}(a)-(1-a)^2R_{n-2}(a)=a(1-a)-a(1-a)^{n-1}(1-a) \quad\cdots\cdots(2)$

$$(1-a)^2R_{n-2}(a)-(1-a)^3R_{n-3}(a)=a(1-a)-a(1-a)^{n-2}(1-a)^2\cdots\cdots(3)$$

$$+)\quad (1-a)^{n-1}R_1(a)-(1-a)^nR_0(a)=a(1-a)^{n-1}-a(1-a)(1-a)^{n-1}\ (n-1)$$

when both sides of above equations from (1) to (n-1) are added together,

$$R_n(a)-(1-a)^nR_0(a)=a\sum_{n=0}^{n-1}(1-a)^n-na(1-a)^n$$

while $R_0(a)=0,\quad \sum_{n=0}^{n-1}(1-a)=\dfrac{1-(1-a)^n}{1-(1-a)}$

so we can obtain $R_n(a)=1-(1-a)^n-na(1-a)^n$

$$R_n(a)=1-(1-a)^n(1+na)\cdots\cdots\cdots\cdots\cdots\cdots\cdots(B)$$

R (a), given by the mathematical formura (B), represents the positive rate of the total number of individuals at (n) years of age, who have experienced exogenous reinfection more than twice during (n) years after birth, but it doesn't mean the development of actual foci in the lungs by exogenous reinfection, because $R_n(a)$ is calculated under the supposition that the infectious rate by exogenous reinfection is the same as that by primary infection, though on account of conceivable influences of immunity or allergic states of the body the formation of the anatomical foci by exogenous reinfection is believed to occur usually less frequently by primary infection. In other words, $R_n(a)$ means the positive rate of the total number of individuals at (n) years of age who have the chances of inhalating tubercle bacilli more than twice during (n) years after birth.

If the total number of individuals at (n) years of age who have exogenous infection over three times during (n) years after birth under the definite infection rate (a) is designed as $T_n(a)$, it can be understood that the following mathematical equations are correct likewise the similar consideration by the induction of $R_n(a)$.

$T_n(a=)T_{n-1}(a)$ …………………	number of individuals who have already infecred exogenously more than three times before the end of (n-1) years of age after birth.
$+a[R_{n-1}(a)-T_{n-1}(a)]$ ……	number of individuals who have the third exogenous infection during the course of a year from (n-1) to (n) years of age among people who already had the first and second tuberculous infection before the end of (n-1) years of age after birth.

$+a^2[P_{n-1}(a)-R_{n-1}(a)]\cdots\cdots$ number of individuals who have the second and third exogenous infections during the course of a year from (n-1) to (n) years of age among people who already had the first tuberculous infection until the end of (n-1) years of age after birth.

$+a^3[1-P_{n-1}(a)]\cdots\cdots\cdots\cdots\cdots$ number of individuals who have three times of exogonous tuberculous infection during the course of a year from (n-1) to (n) years of age among people who had never been infected with tuberculosis until the end of (n-1) years of age after birth.

$$=T_{n-1}(a)+a[R_{n-1}(a)+a\{P_{n-1}(a)-R_{n-1}(a)\}+a^2\{1-P_{n-1}(a)\}-T_{n-1}(a)]$$

$$T_n(a)=T_{n-1}(a)+a[R_n(a)-T_{n-1}(a)]$$

$$\{\because R_{n-1}(a)+a[P_{n-1}(a)-R_{n-1}(a)]+a^2[1-P_{n-1}(a)]=R_n(a)\}$$

$$T_n(a)=T_{n-1}(a)+a\{1-(1-a)^n(1+na)-T_{n-1}(a)\}$$

$$=a-a(1-a)^n(1+na)+(1-a)T_{n-1}(a)$$

hence,

$$T_n(a)-(1-a)T_{n-1}(a)=a-a(1-a)^n-na^2(1-a)^n \cdots\cdots\cdots(1)'$$

$$(1-a)T_{n-1}(a)-(1-a)^2T_{n-2}(a)=a(1-a)-a(1-a)^{n-1}(1-a)-(n-1)a^2(1-a)^{n-1}(1-a)\cdots(2)'$$

$$(1-a)^2T_{n-2}(a)-(1-a)^3T_{n-3}(a)=a(1-a)^2-a(1-a)^{n-2}(1-a)^2-(n-2)a^2(1-a)^{n-2}(1-a)^2\cdots(3)'$$

$$(1-a)^{n-1}T_1(a)-(1-a)^nT_0(a)=a(1-a)^{n-1}-a(1-a)(1-a)^{n-1}-(1)a^2(1-a)(1-a)^{n-1}\cdots(n-1)'$$

when both sides of above equations from (1)′ to (n-1)′ are added together,

$$T_n(a)-(1-a)^nT_0(a)=a\sum_{n=0}^{n-1}(1-a)-na(1-a)^n-a^2(1-a)^n\sum_{n=1}^{n}n$$

while,

$$T_n(a)=0,\ \sum_{n=0}^{n-1}(1-a)^n=\frac{1-(1-a)^n}{1-(1-a)},\ \sum_{n=1}^{n}n=\frac{n(n+1)}{2}$$

so

$$T_n(a)=1-(1-a)^n-na(1-a)^n-a^2(1-a)^n\frac{n(n+1)}{2}$$

$$T_n(a)=1-(1-a)^n\left\{1+na+\frac{n(n+1)}{2}a^2\right\}\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots(C)$$

$T_n(a)$ given by (C) represents the positive rate in the total number of individuals at (n) years of age who have the chance of inhalation of tubercle bacilli over three times during (n) years after birth, but it does not mean the formation of anatomical tuberculous foci in the lungs by exogenous reinfection more than three times.

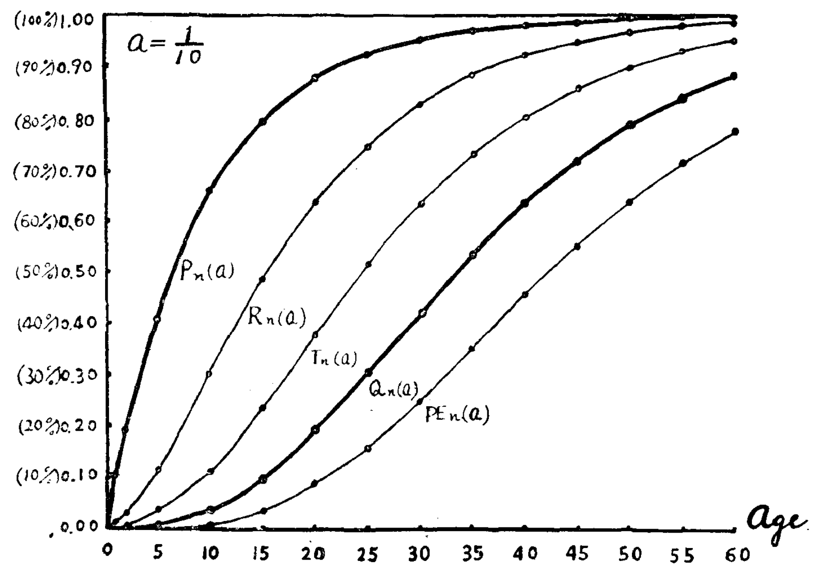
In the same manner we also get the $Q_n(a)$ and $PE_n(a)$ as the equation representing the positive rate in the total number of individuals at (n) years of age who have the chance of inhalation of tubercle bacilli over four and five times during (n) years after birth.

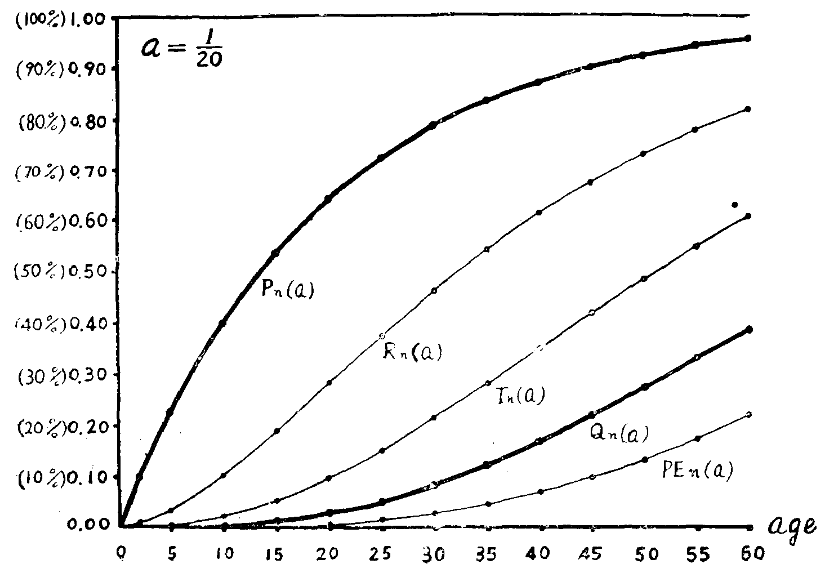
$$Q_n(a)=1-(1-a)^n\left[1+na+\frac{n(n+1)}{2}a^2+\frac{n(n+1)(n+2)}{3.2}a^3\right]\cdots\cdots\cdots\cdots\cdots\cdots(D)$$

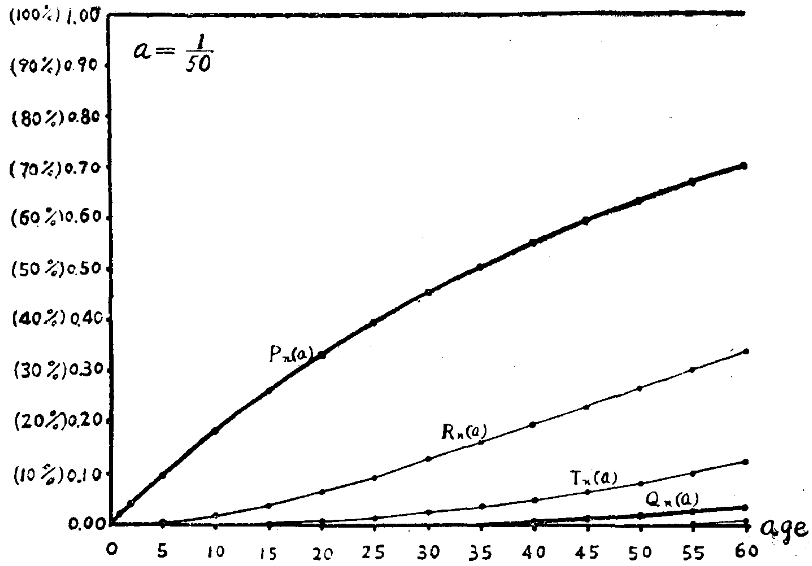
$$PE_n(a)=1-(1-a)^n\left[1+na+\frac{n(n+1)}{2}a^2+\frac{n(n+1)(n+2)}{3.2}a^3\right.$$
$$\left.+\frac{n(n+1)(n+2)(n+3)}{4.3.2}a^4\right]\cdots\cdots\cdots\cdots\cdots\cdots(E)$$

Yearly change of each value of P (a), R (a), T (a), Q (a) and PE (a), calculated by the assumption that the rate of infectious danger per year is respectively $\frac{1}{10}$, $\frac{1}{20}$ and $\frac{1}{50}$, are represented in figure 2.

Figure 2.
Yearly change of each value of $P_n(a)$, $R_n(a)$, $T_n(a)$, $Q_n(a)$ and $PE_n(a)$.







We can also note the following mathematical facts; the duration of ages, which $R_n(a)$ can reach until a half value of $P_n(a)$, is about 12 years after birth by the infectious rate $\frac{1}{10}$, about 24 years by $\frac{1}{20}$, and about 62 years by $\frac{1}{50}$.

Arithmatical means of $P_n(a)$ and $R_n(a)$ in the adult age group (from 20 to 50 years) by each condition that (a) is respectively $\frac{1}{10}$, $\frac{1}{15}$ $\frac{1}{20}$, and $\frac{1}{50}$, are calculated and shown in table 5.

Table 5.
Arithmetical means of P (a) R (a) and T (a) in the adult age-group from 20 to 59 years.

infectious rate per year, (a)	$\frac{1}{10}$	$\frac{1}{15}$	$\frac{1}{20}$	$\frac{1}{50}$
arithmetical means of P(a) in adults	0.970	0.912	0.844	0.538
arithmetical means of R(a) in adults	0.866	0.726	0.585	0.194
arithmetical means of R(a) / arithmetical means of P(a)	0.890	0.79	0.69	0.36

From above stated mathematical treatments we can admit that the positive rate of individuals who have the chances of exogenous reinfection more than twice becomes conspicuously large even in the adolescent age-group, and it increases very strikingly in the adult and advanced ages by the widespreading condition as the rate of tuberculous infection is fairly large, for instance, $\frac{1}{10}$ or $\frac{1}{15}$. We may assume that the same condition existed in large cities in U.S.A. and Europe in the past.

It is said that Kyoto is one of the cities with the greatest tuberculous infection rate in Japan, but the infection rate with tuberculosis is deduced as about $\frac{1}{20}$, which is somewhat smaller than that of large cities in U.S.A. and Europe in the past, and larger than that of semi-rural districts of Sumatra and U.S.A. (Hagerstown, Maryland). We can also admit that in such a similar condition as Kyoto city the positive rate of individuals who already had the chance of exogenous reinfection is deduced to be small in the infant and adolescent ages, but it becomes large in the adult and reachs a high value in the advanced ages.

However, the positive rate above stated is assumed to be commonly small even in the adult and advanced ages in the rural and semi-rural districts, where the rate of infection with tuberculosis per year is very small $\left(\frac{1}{50}\right)$.

Summary

(1) Tuberculous lesions were detected by pathological-anatomical studies in the victims of unnatural death in Kyoto city at the rate of 38% in childhood (from birth to 14 years old), at 58% in the adolescent age-group (from 15 to 19 years old) and at 82% in adult and advanced ages (20 years and over).

According to studies on the properties of the primary complex of anatomical tuberculosis primary infections in the adult and advanced age groups are apparently not rare in Japan, but occur usually at the same or even greater frequency than in chidhood and adolescence.

(2) The positive rate of total individuals who have experienced primary infection during (n) years after birth under the definite infection rate per year (a) is given by the formula $P_n(a)=1-(1-a)$

From the results of anatomical tuberculosis and tuberculin test in Kyoto city it is induced that the rate of infection with tuberculosis per year among the popultion in Kyoto city is about $\frac{1}{20}$. While the rate of infection with tuberculosis per year in a typical and semi-rural district (Oomi-Hachiman town and neighbours) in Japan is apparently about $\frac{1}{50}$ or less,

(3) The positive rate of total individuals at (n) years old in population, who had chances of exogenous reinfection more than twice during (n) years after birth under definite infection rate per years (a), given by the following mathematical formula; $R_n(a)=1-(1-a)^n(1+na)$

By calculation of this mathematical formula it can be deduced that the total individuals, who had chances of exogenous reinfection or superinfection more than twice, appear even during adolescence and they increase strikingly in the advanced age-groups under conditions in which tuberculosis can be widly spread as has been noticed in large cities in U.S.A. and Europe in the past, where the dangerous rate of infection per years is deduced to be about $\frac{1}{10}$ or $\frac{1}{15}$. But it is ordinarily low even in the adult and advanced age-groups in the rural or semi-rural district.s, where the rate of infection per year is very small $\left(\frac{1}{50}\right.$ or below it.$\left.\right)$

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